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>>>Get immediate new with Dialog' Firt Releae
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   broad spectrum of news wires.

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     >>>    of new databases, price changes, etc.      <<<
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File   1:ERIC  1966-2001/Oct 04
       (c) format only 2001 The Dialog Corporation

      Set  Items  Description
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Cost is in DialUnits
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>>>'IALOG' not recognized as set or accession number
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       12oct01 12:02:14 User208760 Session D1959.1
            $0.49    0.141 DialUnits File1
     $0.49  Estimated cost File1
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     $0.54  Estimated cost this search
     $0.54  Estimated total session cost   0.141 DialUnits

File 410:Chronolog(R)  1981-2001/Oct
       (c) 2001 The Dialog Corporation

      Set  Items  Description
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HILIGHT set on as ''
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     $0.00  Estimated cost File410
     $0.01  TYMNET
     $0.01  Estimated cost this search
     $0.55  Estimated total session cost   0.206 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R)  1969-2001/Oct W1
         (c) 2001 BIOSIS
  File  73:EMBASE  1974-2001/Oct W1
         (c) 2001 Elsevier Science B.V.
*File  73: For information about Explode feature please
see Help News73.
  File 155:MEDLINE(R)  1966-2001/Nov W1
  File 399:CA SEARCH(R)  1967-2001/UD=13516
         (c) 2001 AMERICAN CHEMICAL SOCIETY
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*File 399: Use is subject to the terms of your user/customer agreement.
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      Set  Items  Description
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? s (b7(w)2)(20n)(therap? or treat? or vivo or inhibit? or suppress? or
administ?)

Processing
Processing
Processing
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          14521  B7
        7866803  2
        4969412  THERAP?
        5353176  TREAT?
         947696  VIVO
        3342644  INHIBIT?
         666182  SUPPRESS?
        2925970  ADMINIST?
      S1     951  (B7(W)2)(20N)(THERAP? OR TREAT? OR VIVO OR INHIBIT? OR
                  SUPPRESS? OR ADMINIST?)
? s s1 and soluble(W)b7(w)2

           951  S1
        345682  SOLUBLE
         14521  B7
        7866803  2
             1  SOLUBLE(W)B7(W)2
      S2     0  S1 AND SOLUBLE(W)B7(W)2
? s s1 and (b7(w)2)(10n)(soluble or fusion(w)protein?)

Processing
           951  S1
         14521  B7
        7866803  2
         345682  SOLUBLE
         330341  FUSION
        4861256  PROTEIN?
          85272  FUSION(W)PROTEIN?
            115  B7(W)2(10N)(SOLUBLE OR FUSION(W)PROTEIN?)
      S3     49  S1 AND (B7(W)2)(10N)(SOLUBLE OR FUSION(W)PROTEIN?)
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      S4     24  RD S3 (unique items)
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 4/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13104381   BIOSIS NO.: 200100311530
Therapeutic efficacy of ICOS/GL50 (B7h) T cell costimulatory pathway in
  tumor models.
AUTHOR: Zuberek Krystyna(a); Ling Vincent(a); Wu Paul(a); Runyon Kathlene
  (a); Leonard John(a); Collins Mary(a); Dunussi-Joannopoulos Kyri(a)
AUTHOR ADDRESS: (a)Immunology Department, Genetics Institute, Wyeth-Ayerst
  Research, Cambridge, MA**USA
JOURNAL: Blood  96 (11 Part 1):p239a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of
Hematology  San Francisco, California, USA  December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: T cell activation requires costimulation in addition to T cell antigen receptor stimulation for generation of Ag-specific immune responses. To date, two major costimulatory receptor-ligand pairs have been discovered, the extensively studied CD28/B7 pathway and the very recently described ICOS/GL50 (B7h) pathway. We have previously shown that enhancing T cell activation through CD28/B7 costimulation leads to efficacious antitumor activity in murine tumor models. As of yet, the role of ICOS/GL50 costimulation in the generation of antitumor responses has not been reported. In this study we compared the relative efficacy between ICOS/GL50 and CD28/B7 costimulation in head-to-head experiments in various murine tumor models. For systemic **treatment** of tumors, we generated murine **B7.2**-IgG and GL50-IgG **fusion proteins**, consisting of the extracellular domain of **B7.2** or GL50 and the Fc portion of murine IgG2a. Murine isotype IgG2a was used as control. Mice bearing MethA or B16F1 melanoma tumors were **treated** sc with 50ug/injection of GL50-IgG or **B7.2**-IgG, twice weekly for three weeks. In the MethA model, **treatment** with **B7.2**-IgG resulted in 100% tumor regression and cure of mice, and **treatment** with GL50-IgG resulted in 60% cure and in 40% significant tumor growth delay. In the B16F1 melanoma, systemic treatment with either protein led to comparable significant tumor growth delay. In both tumor models, IgG2a treatment had no effect. In tumor vaccines studies, the B16F1 melanoma and the MB49 bladder carcinoma models were used. Tumor cells were transduced with a vector containing the EF-1 alpha promoter expressing either murine B7.1 or GL50, and were used for in vivo tumorigenicity experiments. Our results demonstrate: (i) in the B16F1 model, 40% of the mice injected with GL50 expressing tumor cells and 20% of the mice injected with B7.1 expressing tumor cells reject their tumors; (ii) in the MB49 model, 30% of the mice injected with GL50 expressing tumor cells and 10% of the mice injected with B7.1 expressing tumor cells reject their tumors. These preliminary results indicate that enhanced in vivo ICOS/GL50 interactions, provided either by soluble GL50-IgG or GL50 expression on tumor cells, has significant antitumor activity that is comparable to the well described antitumor efficacy of the CD28/B7 pathway in murine tumor models.

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12246315 BIOSIS NO.: 199900541164
Potent activity of soluble B7-IgG fusion proteins in therapy of established tumors and as vaccine adjuvant.
AUTHOR: Sturmhoefel Knut(a); Lee Kwang; Gray Gary S; Thomas Jenifer; Zollner Richard; O'Toole Margot; Swiniarski Holly; Dorner Andrew; Wolf Stanley F
AUTHOR ADDRESS: (a)Lexigen Pharmaceuticals, 125 Hartwell Avenue, Lexington, MA, 02421-3125**USA
JOURNAL: Cancer Research 59 (19):p4964-4972 Oct. 1, 1999
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Fusion** proteins consisting of the extracellular region of murine B7.1 or **B7.2** and the Fc portion of murine IgG2a (B7-IgG) were evaluated for their ability to promote antitumor responses. **Therapeutic administration** of soluble B7-IgG in mice with established tumors induced complete regression of the tumor and increased the survival of mice. In three models, MethA, P815, and MB49, mice with

7-day-old established tumors were cured with two to three treatment cycles of B7-IgG, given twice a week. Even in mice with an established B16/F10 tumor (a poorly immunogenic melanoma), therapeutic treatment with B7-IgG alone slowed tumor growth and increased survival significantly. Still stronger antitumor activity was achieved when B7-IgG was used as a vaccine adjuvant mixed with irradiated tumor cells. In 80% of mice with 7-day-old B16 tumors, tumors regressed completely, and mice survived for at least 80 days. In all tumor models, B7.1-IgG and B7.2-IgG had similar antitumor activity. B7-IgG-mediated tumor rejection was dependent on T cells, specifically CD8 cells, as demonstrated by the failure of B7-IgG to induce tumor regression in severe combined immunodeficient or CD8-depleted mice. In addition, mice that were cured of an established tumor were protected against a rechallenge with the same tumor for at least 4 months, suggesting the generation of memory responses. Surprisingly, the antitumor activity of B7-IgG was independent of IFN-gamma, as demonstrated by tumor rejection in IFN-gamma knockout mice. Our findings demonstrate the potent capacity of B7-IgG to generate or enhance antitumor immune responses and suggest the clinical value of B7-IgG.

4/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12203408 BIOSIS NO.: 199900498257
Immune response enhancement by in vivo administration of B7.2Ig, a soluble costimulatory protein.
AUTHOR: Swiniarski Holly; Sturmhoefel Knut; Lee Kwang; Gray Gary S; Thomas Jenifer L; Wolf Stanley F; Dorner Andrew J; O'Toole Margot(a)
AUTHOR ADDRESS: (a)Genetics Institute, One Burtt Road, Andover, MA, 01810** USA
JOURNAL: Clinical Immunology (Orlando) 92 (3):p235-245 Sept., 1999
ISSN: 1521-6616
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The identification of both class I- and class II-restricted tumor-associated peptides recognized by T cells has led to the test of these peptides as immunogens in experimental immunotherapy for cancer patients. However, optimal T cell activation requires signaling both through the T cell receptor for antigen and through costimulatory pathways. B7.1 and B7.2 are powerful costimulatory molecules expressed on the surface of antigen-presenting cells. Using a mouse model, we have sought to optimize costimulatory signals during antipeptide responses by **administering** a **soluble** form of **B7.2** at the time of peptide immunization. **Administration** of B7.2Ig **fusion protein** significantly enhanced T helper cell and CTL responses. These findings suggest that **soluble** forms of human **B7.2** protein may provide a straightforward and practical method of supplying optimal costimulation during clinical immunotherapy.

4/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12028015 BIOSIS NO.: 199900308534
Induction of therapeutic T-cell immunity by tumor targeting with soluble recombinant B7-immunoglobulin costimulatory molecules.
AUTHOR: Moro Monica; Gasparri Anna Maria; Pagano Stefano; Bellone Matteo; Tornaghi Paola; Veglia Fabrizio; Corti Angelo; Casorati Giulia; Dellabona Paolo(a)
AUTHOR ADDRESS: (a)Unita d'Immunochimica, DIBIT, Istituto Scientifico San

Raffaele, Via Olgettina 58, Milan, 20132**Italy
JOURNAL: Cancer Research 59 (11):p2650-2656 June 1, 1999
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Tumor targeting with immunomodulatory molecules is an attractive strategy to enhance the host's antitumor response. Expression of CD80 (B7-1) and CD86 (B7-2) costimulatory molecules in tumor cells has proven to be an efficient way to enhance their immunogenicity. Here, we studied the effects of tumor targeting with biotinylated recombinant **soluble** B7-1- and **B7-2** immunoglobulin G molecules (bio-B7-IgG) using a pretargeting approach based on the sequential use of a biotinylated antitumor monoclonal antibody and avidin. Mouse RMA T-lymphoma cells bearing either bio-B7-1-IgG or bio-**B7-2**-IgG on their surface prime in vitro naive CD8+ CTLs, which are highly effective in adoptive immunotherapy, and induce **therapeutic** immunity when injected in tumor-bearing animals. In vivo targeting of established RMA tumors with bio-B7-IgG either cures tumor-bearing mice or significantly prolongs their survival. The antitumor response induced by targeted bio-B7-IgG depends on both CD4+ and CD8+ T cells. Moreover, tumor targeting with bio-B7-IgG in vivo is critical for both expansion in lymphoid organs and mobilization into the tumor of tumor-specific CD8+ CTLs. When targeting is performed on poorly immunogenic TS/A mammary adenocarcinoma, only bio-B7-1-IgG primes naive CTLs in vitro and cures or significantly prolongs the survival of tumor-bearing mice in vivo, confirming that the two costimulatory molecules are not redundant with this tumor. Altogether, these data suggest that tumor avidination and targeting with soluble bio-B7-IgG may represent a promising strategy to enhance the antitumor response in the host.

4/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11023791 BIOSIS NO.: 199799644936
The IgV domain of human B7-2 (CD86) is sufficient to co-stimulate T lymphocytes and induce cytokine secretion.
AUTHOR: Rennert Paul(a); Furlong Kimberly; Jellis Cindy; Greenfield Edward; Freeman Gordon J; Ueda Yuji; Levine Bruce; June Carl H; Gray Gary S
AUTHOR ADDRESS: (a)Biogen Inc., 14 Cambridge Center, Cambridge, MA 02142** USA
JOURNAL: International Immunology 9 (6):p805-813 1997
ISSN: 0953-8178
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: B7-1 (CD80) and B7-2 (CD86) are genetically and structurally related molecules expressed on antigen-presenting cells. Both bind CD28 to co-stimulate T lymphocytes, resulting in proliferation and cytokine production. The extracellular portions of B7-1 and B7-2 which bind to CD28 and CTLA-4 are related to Ig variable (V) and Ig constant (C) domain sequences. Recent reports have described splice variant forms of B7 proteins which occur in **vivo** and are of unknown function. Here we describe **soluble** recombinant forms of B7-1 and **B7-2** containing either both of the Ig-like extracellular domains or the individual IgV or IgC domains coupled to an Ig Fc tail. **Soluble** B7-1 and **B7-2** bind to CD28 and CTLA-4, and effectively co-stimulate T lymphocytes resulting in their proliferation and the secretion of cytokines. Furthermore, the IgV domain of B7-2 binds CD28 and CTLA-4, competes with B7-1 and B7-2 for binding to these receptors, and co-stimulates T lymphocytes. Cross-linked soluble B7-2v was the most potent co-stimulatory molecule tested and was active at a concentration

-100-fold lower than cross-linked **soluble** B7-1 or **B7-2** proteins. When bound to tosyl-activated beads, B7-2v was capable of sustaining multiple rounds of T cell expansion. These data complement the description of naturally occurring variants to suggest that T cell co-stimulation in vivo may be regulated by soluble or truncated forms of B7 proteins.

4/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10945301 BIOSIS NO.: 199799566446
In situ expression of B7 and CD28 receptor families in skin lesions of patients with lupus erythematosus.
AUTHOR: Denfeld Ralf W(a); Kind Peter; Sontheimer Richard D; Schoepf Erwin; Simon Jan C
AUTHOR ADDRESS: (a)Univ. Freiburg, Dep. Dermatology, Hauptstrasse 7, 79104 Freiburg**Germany
JOURNAL: Arthritis & Rheumatism 40 (5):p814-821 1997
ISSN: 0004-3591
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective. To examine the expression of costimulatory molecules of the B7 and CD28 receptor families in active skin lesions of patients with systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus (SCLE), and chronic discoid lupus erythematosus (CDLE). Methods. The in situ expression of B7-1, B7-2, BB-1, and CD28 was studied by immunohistochemistry, and B7-1 and B7-2 RNA expression was examined by reverse transcription-polymerase chain reaction. Results. Only in lesional skin from SLE, SCLE, and CDLE patients did dermal and epidermal antigen-presenting cells (APC) express B7-1 and B7-2, particularly when in apposition to CD28+ T cells. These B7-1+ and **B7-2**+ APC bound CTLA-4 **fusion protein**. In lesional (but not in nonlesional) skin, keratinocytes expressed BB-1. The majority of infiltrating T cells were CD28+. B7-1 and B7-2 RNA were expressed in lesional skin from SLE, SCLE, and CDLE patients; when dermis was separated from epidermis, only faint B7-1 and B7-2 RNA signals were detectable in the epidermis, indicating that dermal but not epidermal cells were the major source of B7-1 and **B7-2** RNA. During **treatment**, both B7-1 and **B7-2** protein and RNA expression were reduced. Conclusion. These in situ findings suggest that costimulation via the B7-CD28 pathway may be important for the generation and/or propagation of T cell activity in skin lesions of humans with lupus erythematosus. Thus, the manipulation of this pathway (e.g., by CTLA-4 fusion protein) could be an important target for the development of future therapies for LE.

4/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10273323 BIOSIS NO.: 199698728241
Expression and function of B7-1 (CD80) and B7-2 (CD86) on human epidermal Langerhans cells.
AUTHOR: Rattis Frederique-Marie(a); Peguet-Navarro Josette; Staquet Marie-Jeanne; Dezutter-Dambuyant Colette; Courtellemont Pascal; Redziniak Gerard; Schmitt Daniel
AUTHOR ADDRESS: (a)INSERM U346, Pavillon R. Hopital E. Herriot, F-69437 Lyon Cedex 03**France
JOURNAL: European Journal of Immunology 26 (2):p449-453 1996
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: In addition to T cell receptor triggering, activation of T cells requires co-stimulatory signals that have been shown to be mainly initiated through CD28. We analyzed the expression and function of the two ligands for CD28, B7-1 (CD80) and B7-2 (CD86), on human Langerhans cells (LC), the antigen-presenting cells from epidermis. Human LC freshly isolated from epidermis (fLC) expressed significant level of B7-2, which was increased upon a short culture in vitro. In contrast, B7-1 was undetectable on fLC but appeared at the cell surface after a 3-day culture in vitro. Pre-incubation of 18-h cultured LC with anti-B7-2 monoclonal antibodies (mAb) was sufficient to abrogate the binding of CTLA4-Ig **fusion** protein, while a combination of both mAb against B7-1 and **B7-2** was necessary to obtain a complete **inhibition** of CTLA4-Ig binding on 3-day cultured LC, showing the absence of a third CTLA4 ligand. The function of B7-1 and B7-2 on human LC has been analyzed by adding mAb at the beginning of mixed epidermal cell lymphocyte reactions. Anti-**B7-2** mAb and CTLA4-Ig, but not anti-B7-1 mAb, strongly **inhibited** allogeneic, as well as recall antigen-induced T cell proliferation supported by fLC or 3-day cultured LC. Collectively, these results demonstrate that B7-2 is the major ligand for CD28/CTLA4 at the LC surface and that it plays a crucial role in human LC co-stimulatory function with little, if any, dependence on B7-1 expression.

4/7/8 (Item 8 from file: 5)

10245652 BIOSIS NO.: 199698700570
In vivo blockade of TNF-alpha by intravenous infusion of a chimeric monoclonal TNF-alpha antibody in patients with rheumatoid arthritis. Short term cellular and molecular effects.
AUTHOR: Lorenz Hanns-Martin(a); Antoni Christian; Valerius Thomas; Repp Roland; Gruenke Mathias; Schwerdtner Nives; Buesslein Hubert; Woody Jim; Kalden Joachim R; Manger Berhard
AUTHOR ADDRESS: (a)Dep. Intern. Med. III, Inst. Clin. Immunol., Univ. Erlangen-Nuremberg, Glueckstrasse 4a, 91054 E**Germany
JOURNAL: Journal of Immunology 156 (4):p1646-1653 1996
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Due to the unknown etiology of RA, specific treatment is not available. Recently, in a double-blinded, placebo-controlled clinical trial, in vivo blockade of TNF-alpha by a single infusion of a chimeric TNF-a-blocking mAb, cA2, has proven to be highly effective in the treatment of RA. In parallel to this trial, we tested the consequences of cA2 infusion in ex vivo and in vitro experiments. In this paper, we describe an increase in CD4+ and CD8+ T lymphocyte counts on day 1 and a marked decrease in monocyte counts preferentially on day 7 after cA2 treatment, without major changes in B lymphocyte or NK cell counts. In addition, we found an increased responsiveness of PBMC to CD28 mAb/PMA, but not to CD3 mAb, superantigen staphylococcus enterotoxin B, or PHA on day 1 after infusion. The increase in DNA synthesis of PBMC was paralleled by increased IL-2 mRNA and IL-4 mRNA expression and IL-2 protein secretion in culture supernatants after in vitro stimulation of PBMC with CD28 mAb/PMA. In PBMC, we did not find any significant changes in mRNA or protein expression of CD28 Ag or CD28 ligands, B7-1 and **B7-2**. Serum concentrations of IL-1-beta, IL-6, and **soluble** CD14 were significantly diminished after in **vivo** TNF-alpha blockade. We did not see relevant changes in granulocyte function in vitro after cA2 infusion. Finally, we observed a statistically significant decrease in sICAM-1 molecules in the serum of

patients treated with verum compared with that in the serum of subjects given placebo. This change in sICAM-1 concentration was evident on days 1 and 7 after the infusion of 10 mg/kg cA2, whereas it occurred only on day 7 in the serum of patients treated with the low dose (1 mg/kg) of cA2.

4/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10108722 BIOSIS NO.: 199698563640
Alloantigen presentation by B cells: Analysis of the requirement for B-cell activation.
AUTHOR: Wilson J L; Cunningham A C; Kirby J A(a)
AUTHOR ADDRESS: (a)Dep. Surg., Med. Surg., Univ. Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH**UK
JOURNAL: Immunology 86 (3):p325-330 1995
ISSN: 0019-2805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This paper describes a model for investigation of the functional implications of B-cell activation for antigen presentation. Mixed lymphocyte cultures were used to assess the ability of freshly isolated B cells, mitogen-activated B cells and Epstein-Barr virus (EBV)-transformed B-cell lines to stimulate the activation and proliferation of allogeneic T cells under a variety of experimental conditions. It was found that resting B cells presented antigen poorly, while activated cells were highly immunogenic. Paraformaldehyde fixation completely eliminated antigen presentation by resting B cells, despite constitutive expression of class II MHC antigens. However, fixation had little effect on antigen presentation by activated B cells that expressed B7-1 and **B7-2** in addition to class II major histocompatibility complex (MHC) molecules. Arrest of B-cell activation by serial fixation after **treatment** with F(ab')-2 fragments of goat anti-human IgM produced cells with variable antigen-presenting capacity. Optimal antigen presentation was observed for cells fixed 72-hr after the initiation of B-cell activation. Although both B7-1 and B7-2 antigen expression increased after B-cell activation, it was found that the rate of T-cell proliferation correlated most closely with B7-2 expression. Stimulation of T cells by fixed activated B lymphocytes could be blocked by antibodies directed at class II MHC molecules, indicating involvement of the T-cell antigen receptor. In addition, T-cell proliferation was **inhibited** by antibodies specific for B7-1 and **B7-2** and by the **fusion protein** CTLA4-Ig, demonstrating a requirement for CD28 signal transduction. The sole requirement of B7 family expression for antigen presentation by B lymphocytes was shown by demonstration of T-cell stimulation by fixed resting B cells in the presence of CD28 antibody as a source of artificial costimulation.

4/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10044596 BIOSIS NO.: 199598499514
Influence of MHC class I molecules on T-cell proliferation induced by CD3 or thy-1 stimulation.
AUTHOR: Amirayan N; Furrie E; Deleuil F; Mellor A; Leserman L; Machy P(a)
AUTHOR ADDRESS: (a)Cent. d'Immunol. INSERM-CNRS de Marseille-Luminy, Case 906, 13288 Marseille Cedex 9**France
JOURNAL: Immunology 86 (1):p71-78 1995
ISSN: 0019-2805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: We have reported that class I- (and lymphocyte function-associated antigen-1 (LFA-1-)) specific monoclonal antibodies (mAb) inhibit anti-CD3-mediated activation of naive T cells. The present study investigated the mechanism of this inhibition. CD28-specific mAb augmented stimulation induced by soluble CD3 mAb, but this costimulation was also inhibited by anti-class I or anti-LFA-1 mAb. However, stimulation of T cells was not **inhibited** when activated B cells were present. Neither B7-1- nor **B7-2**-specific blocking mAb or **soluble** CTLA-4, CD40 or gp39 restored the **inhibition**. Thus, other molecules expressed on activated B cells are implicated for T-cell activation, which could compensate blockade of class I or LFA-1 molecules. Inhibition induced by class I-specific mAb could potentially be mediated through extracellular, transmembrane or cytoplasmic domains of the target molecules. These possibilities were evaluated by the use of mice transgenic for the Qa-2 molecule, selected for expression of Qa-2 at levels equivalent to classical class I molecules. Qa-2 is inserted in the membrane through phosphatidylinositol linkages. Antibodies directed to Qa-2 inhibited CD3-induced stimulation, demonstrating that cytoplasmic and transmembrane protein sequences of class I molecules are not necessary for the inhibitory effect. Inhibition thus presumably depends on extracellular domains. Finally, T cells from beta-2-microglobulin knock-out mice responded to CD3-specific mAb as well as their class I-positive littermates. Nevertheless, stimulation of T cells from these mice with mitogenic anti-Thy-1 mAb was markedly reduced. Signalling by Thy-1 and the CD3 complex may normally occur through pathways in which class I molecules are implicated.

4/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09732031 BIOSIS NO.: 199598186949
Differential Effects of Anti-B7-1 and Anti-**B7-2** Monoclonal Antibody **Treatment** on the Development of Diabetes in the Nonobese Diabetic Mouse.
AUTHOR: Lenschow Deborah J; Ho Stephen C; Sattar Husain; Rhee Lesley; Gray Gary; Nabavi Nasrin; Herold Kevan C; Bluestone Jeffrey A(a)
AUTHOR ADDRESS: (a)Ben May Inst., Univ. Chicago, MC1089, 5841 S. Maryland Ave., Chicago, IL 60637**USA
JOURNAL: Journal of Experimental Medicine 181 (3):p1145-1155 1995
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Insulin-dependent diabetes mellitus (IDDM) is thought to be an immunologically mediated disease resulting in the complete destruction of the insulin-producing islets of Langerhans. It has become increasingly clear that autoreactive T cells play a major role in the development and progression of this disease. In this study, we examined the role of the CD28/B7 costimulation pathway in the development and progression of autoimmune diabetes in the nonobese diabetic (NOD) mouse model. Female NOD mice treated at the onset of insulitis (2-4 wk of age) with CTLA4Ig immunoglobulin (Ig) (a **soluble** CD28 antagonist) or a monoclonal antibody (mAb) specific for **B7-2** (a CD28 ligand) did not develop diabetes. However, neither of these **treatments** altered the disease process when **administered** late, at gt 10 wk of age. Histological examination of islets from the various **treatment** groups showed that while CTLA41g and anti-**B7-2** mAb **treatment** blocked the development of diabetes, these reagents had little effect on the development or severity of insulitis. Together these results suggest that blockade of costimulatory signals by CTLA4Ig or anti-**B7-2** acts early in disease development, after insulitis

but before the onset of frank diabetes. NOD mice were also **treated** with mAbs to another CD28 ligand, B7-1. In contrast to the previous results, the anti-B7-1 treatment significantly accelerated the development of disease in female mice and, most interestingly, induced diabetes in normally resistant male mice. A combination of anti-B7-1 and anti-**B7-2** mAbs also resulted in an accelerated onset of diabetes, similar to that observed with anti-B7-1 mAb **treatment** alone, suggesting that anti-B7-1 mAb's effect was dominant. Furthermore, treatment with anti-B7-1 mAbs resulted in a more rapid and severe infiltrate. Finally, T cells isolated from the pancreases of these anti-B7-1-treated animals exhibited a more activated phenotype than T cells isolated from any of the other treatment groups. These studies demonstrate that costimulatory signals play an important role in the autoimmune process, and that different members of the B7 family have distinct regulatory functions during the development of autoimmune diabetes.

4/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09731962 BIOSIS NO.: 199598186880
Studies on the interdependence of gp39 and B7 expression and function during antigen-specific immune responses.
AUTHOR: Roy Meenakshi; Aruffo Alejandro; Ledbetter Jeffrey; Linsley Peter; Kehry Marilyn; Noelle Randolph(a)
AUTHOR ADDRESS: (a)Dep. Microbiol., Dartmouth Med. Sch., 1 Medical Center Drive, Lebanon, NH 03756**USA
JOURNAL: European Journal of Immunology 25 (2):p596-603 1995
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interactions between T and B cells are dynamic and regulated by interacting, receptor: co-receptors. Interactions between CD40 and its ligand, gp39, and the CD28/CTLA-4 and B7 family members play a decisive role in regulating the progression of cognate interactions. The interdependence of gp39-CD40 and CD28/CTLA-B7 expression and function was studied in vitro during an antigeninduced immune response using T cells from mice expressing a transgenic T cell receptor (TCR). gp39 was induced on pigeon cytochrome c (PCC)-transgenic T cells in the presence of antigen and antigen-presenting cells. The antigeninduced expression of gp39 on transgenic T cells was inhibited by antibodies to class II major histocompatibility complex, CD4 and LFA-1, but not by CTLA-4 Ig, anti-B7-1 or anti-B7-2. These data established that the antigen-induced expression of gp39 was not dependent on co-stimulation via CD28/CTLA-4. The addition of PCC also resulted in the modest expression of B7-1 and a more robust expression of B7-2 on the cognate B cells. The addition of anti-gp39 blocked the up-regulated expression of B7-1 and partially blocked the up-regulated expression of **B7-2**. The addition of anti-gp39 and anti-interleukin-4 **inhibited** antigeninduced expression of **B7-2** on B cells to near background levels. Studies on the up-regulation of B7-1 and **B7-2** on resting B cells showed that **soluble** gp39 up-regulated B7-1 and **B7-2** expression on B cells. In addition, interleukin-4 and interferon-gamma up-regulated B7-2 expression on B cells. Taken together, these data demonstrate that the antigen-induced expression of gp39 is dependent on TCR-derived signals, yet independent of CD28/CTLA-4 co-stimulatory signals. Cognate interactions also resulted in the modest enhancement of B7-1 expression and a more profound expression of B7-2 which were completely or partially dependent on gp39-CD40 interactions.

4/7/13 (Item 13 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

09580670 BIOSIS NO.: 199598035588
B70/B7-2 is identical to CD86 and is the major functional ligand for CD28 expressed on human dendritic cells.
AUTHOR: Caux Christophe(a); Vanbervliet Beatrice; Massacrier Catherine; Azuma Miyuki; Okumura Ko; Lanier Lewis L; Banchereau Jacques
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JOURNAL: Journal of Experimental Medicine 180 (5):p1841-1847 1994
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Dendritic cells comprise a system of highly efficient antigen-presenting cells involved in the initiation of T cell responses. Herein, we investigated the role of the CD28 pathway during alloreactive T cell proliferation induced by dendritic-Langerhans cells (D-Lc) generated by culturing human cord blood CD34+ progenitor cells with granulocyte/macrophage colony-stimulating factor and tumor necrosis factor alpha. in addition to expressing CD80 (B7/BB1), a subset of D-Lc expressed B70/**B7-2**. Binding of the CTLA4-Ig **fusion protein** was completely **inhibited** by a combination of monoclonal antibodies (mAbs) against CD80 and B70/**B7-2**, indicating the absence of expression of a third ligand for CD28/CTLA-4. It is interesting to note that mAbs against CD86 completely prevented the binding of CTLA4-Ig in the presence of mAbs against CD80 and bound to a B70/B7-2-transfected fibroblast cell line, demonstrating that the B70/**B7-2** antigen is identical to CD86. CD28 triggering was essential during D-Lc-induced alloreaction as it was **inhibited** by mAbs against CD28 (9 out of 11 tested). However, none of six anti-CD80 mAbs demonstrated any activity on the D-Lc-induced alloreaction, though some were previously described as inhibitory in assays using CD80-transfected cell lines. In contrast, a mAb against CD86 (IT-2) was found to suppress the D-Lc-dependent alloreaction by 70%. This inhibitory effect was enhanced to gtoreq 90% when a combination of anti-CD80 and anti-CD86 mAbs was used. The present results demonstrate that D-Lc express, in addition to CD80, the other ligand for CTLA-4, CD86 (B70/B72), which plays a primordial role during D-Lc-induced alloreaction.

4/7/14 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06629450 EMBASE No: 1996294255
Preventing allograft rejection with CTLA4IG: Effect of donor-specific transfusion route or timing
Bolling S.F.; Lin H.; Wei R.-Q.; Turka L.A.
Section of Thoracic Surgery, 2120D Taubman Center, University of Michigan Hospitals, 1500 E Medical Center Dr.,Ann Arbor, MI 48109-0344 United States
Journal of Heart and Lung Transplantation (J. HEART LUNG TRANSPLANT.) (United States) 1996, 15/9 (928-935)
CODEN: JHLTE ISSN: 1053-2498
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background: Tolerance to alloantigen in transplant recipients could remove life-long dependence on immunosuppression. Evidence suggests that T-cell responses to alloantigen are dependent not only on T-cell receptor activation but also on costimulation by means of the CD28 receptor. The natural ligands for CD28, expressed on antigen-presenting cells, are B7

family members. CTLA4Ig (a **soluble** CD28 receptor analog) preferentially binds B7-1 and **B7-2** and **inhibits** CD28 activation. Theoretically, T-cell receptor activation in the presence of alloantigen during CTLA4Ig blockade of CD28-B7 costimulation could render T cells tolerant to that specific alloantigen. In vivo CTLA4Ig significantly increases allograft survival times and can lead to transplantation tolerance. In the rat cardiac allograft model, donor-specific transfusion must be combined with CTLA4Ig to induce tolerance. Previously our laboratory has shown that timing is crucial in the induction of tolerance. Methods: We examined the effect of differing routes (intravenous, portal vein, or intrathymic), as well as timing (before, at, and after transplantation), of donor-specific transfusion on its ability to synergize with CTLA4Ig using a rat heterotopic major histocompatibility complex-mismatch heart transplant model. Results: We found that tolerance induced by CTLA4Ig and donor-specific transfusion was antigen specific and that timing, but not route of donor-specific antigen administration, had an impact on tolerance induction. Intravenous donor-specific transfusion had a beneficial effect on allograft survival equal to portal vein and intrathymic routes, which have been believed to be more tolerogenic. Conclusions: Almost universal engraftment can be induced with a combination of intravenous donor- specific transfusion at transplantation plus inhibition of CD28 activation by CTLA4Ig 48 hours after transplantation-a regimen which could have clinical application.

4/7/15 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06482792 EMBASE No: 1996149529
Immunosuppression through blockade of CD28:B7-mediated costimulalory signals
Judge T.A.; Tang A.; Turka L.A.
Institute for Human Gene Therapy, University of Pennsylvania, 422 Curie Boulevard,Philadelphia, PA 19104-6069 United States
Immunologic Research (IMMUNOL. RES.) (Switzerland) 1996, 15/1 (38-49)
CODEN: IMRSE ISSN: 0257-277X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

It is now well established that T cells require two signals for activation and effector function. The first signal is provided through the T cell receptor for antigen. The best-characterized pathway which provides the second, or costimulatory, signal is through the CD28 receptor on the surface of T cells. In vitro, ligation of the T cell receptor without a second signal induces a long-lived state of anergy in T cells. CD28 has two known ligands, B7-1 and **B7-2**, expressed on activated antigen-presenting cells. A soluble **fusion protein** called CTLA4Ig has been produced which binds B7-1 and **B7-2** and acts as a competitive **inhibitor** of CD28. In vitro and in **vivo** studies with CTLA4Ig demonstrate that it is an extremely effective immunosuppressive agent in models of transplantation and autoimmunity. Mechanistic studies indicate that CTLA4Ig may work by partially inhibiting the expansion of antigen-reactive cells and inducing anergy in the residual population.

4/7/16 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11377257 21178696 PMID: 11282992
CTLA-4-Fas ligand functions as a trans signal converter protein in bridging antigen-presenting cells and T cells.
Huang JH; Tykocinski ML
Department of Pathology and Laboratory Medicine, University of Pennsylvania, 6 Gates Pavilion, 3400 Spruce Street, Philadelphia, PA

19104-4283, USA.
International immunology (England) Apr 2001, 13 (4) p529-39, ISSN 0953-8178 Journal Code: AY5
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Co-stimulator blockade and trans inhibitory signaling, using agents such as CTLA-4-Ig and Fas ligand (FasL) respectively have been invoked as alternative strategies for suppressing pathogenic T cells. This study describes a novel hetero-bifunctional fusion protein, CTLA-4-FasL, designed to combine within a single protein both co-stimulator blocking and trans inhibitory signaling potentials. A chimeric expression cassette, in which the ectodomain coding sequences for CTLA-4 and FasL were linked in-frame, was used to produce a CTLA-4-FasL **fusion protein**. CTLA-4-FasL binding to both B7-1/**B7-2** -expressing Daudi B cells and Fas-expressing Jurkat T cells was documented by immunofluorescence and flow cytometry. The capacity of CTLA-4-FasL to induce apoptosis in Jurkat targets was markedly enhanced by the addition of Daudi and other B7-1/B7-2(+) B cell lines, which provided a membrane platform for the otherwise soluble CTLA-4-fusion protein. Moreover, in dual-chamber experiments, Daudi cells pre-coated with CTLA-4-FasL demonstrated Jurkat inhibitory activity that was cell-contact dependent. Significantly, when used to inhibit in vitro cellular proliferation of peripheral blood mononuclear cells, CTLA-4-FasL was approximately 1000-fold more potent than the extensively characterized CTLA-4-Ig fusion protein. Furthermore, the degree of inhibition induced by CTLA-4-FasL substantially surpassed that observed for CTLA-4-Ig and a soluble FasL when used in combination. CTLA-4-FasL represents the first of a novel class of fusion proteins, designated here as 'trans signal converter proteins', that combine trans signal masking and direct trans signaling functions.
Record Date Created: 20010403

4/7/17 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09996688 99077517 PMID: 9862681
Importance of B7-1-expressing host antigen-presenting cells for the eradication of B7-2 transfected P815 tumor cells.
La Motte RN; Sharpe AH; Bluestone JA; Mokyr MB
Department of Biochemistry and Molecular Biology, University of Illinois at Chicago, 60612, USA.
Journal of immunology (UNITED STATES) Dec 15 1998, 161 (12) p6552-8, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: P01 AI-35294, AI, NIAID; R01 CA-76532, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have previously shown that B7-2 (CD86)-transfected P815 tumor cells elicit tumor-eradicating immunity that leads to the regression of the B7-2+ P815 tumor after transient growth in normal DBA/2 mice. Here, we show that both the **B7-2** and B7-1 (CD80) molecules contribute to the eradication of **B7-2**+ P815 tumors as **treatment** of the mice with both anti-**B7-2** and anti-B7-1 mAb was required to prevent **B7-2** + P815 tumor regression. The cells that expressed the B7-1 molecule following inoculation of B7-2+ P815 tumor cells into normal mice were not the tumor cells but rather host APCs including MAC-1+ cells present in the draining lymph nodes. Moreover, B7-1-expressing host APCs were found to be important for the rejection of B7-2+ P815 tumors as anti-B7-2 mAb alone, which was ineffective in preventing B7-2+ P815 tumor rejection by normal wild-type mice, was effective in preventing B7-2+ P815 tumor rejection by mice in which the B7-1 gene was disrupted. Finally, consistent with the importance of B7-1-expressing host APCs for the generation of tumor-eradicating immunity against B7-2+ P815 tumor cells, CD4+ T cells (not only CD8+ T cells) were found to participate in tumor-eradicating immunity against B7-2+ P815 tumor cells. Thus, in

addition to eliciting tumor-eradicating immunity directly, B7-2+ P815 tumor cells elicit tumor-eradicating immunity indirectly through B7-1-expressing host APCs that present tumor-associated Ags to CD4+ T cells.
Record Date Created: 19990122

4/7/18 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09628372 98077533 PMID: 9414288
Gene immunotherapy in murine acute myeloid leukemia: granulocyte-macrophage colony-stimulating factor tumor cell vaccines elicit more potent antitumor immunity compared with B7 family and other cytokine vaccines.
Dunussi-Joannopoulos K; Dranoff G; Weinstein HJ; Ferrara JL; Bierer BE; Croop JM
Dana-Farber Cancer Institute and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
Blood (UNITED STATES) Jan 1 1998, 91 (1) p222-30, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In an attempt to explore novel treatment modalities in acute myeloid leukemia (AML), we studied the role of costimulatory and cytokine gene immunotherapy in murine AML. We have previously shown that leukemic mice can be cured with CD80 transfected leukemic cells (B7. 1-AML vaccine) administered early in the course of the disease and that the failure B7.1-AML vaccines administered late cannot be attributed to immunosuppression induced by tumor growth. CD8+ T cells, which are necessary for tumor rejection, are activated rather than **suppressed** during the first half of the leukemic course in nonvaccinated mice. In this report, we question whether CD86 (**B7.2**) or the cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-4 (IL-4), or tumor necrosis factor-alpha (TNF-alpha) can improve the vaccination potential of AML cells. The choice of cytokines was based on their combined and alone as well ability to direct the differentiation of CD34+ cells into potent antigen-presenting dendritic cells in vitro. Our studies show that (1) mice vaccinated with a leukemogenic number of AML cells engineered to express B7.2 (B7.2-AML) or to secrete GM-CSF, IL-4, or TNF-alpha (GM-, IL-4-, TNF-alpha-AML) do not develop leukemia; (2) GM-AML cells are tumorigenic in sublethally irradiated SJL/J mice but not in Swiss nu/nu mice, indicating that killing of tumor cells is not T-cell-dependent; (3) vaccines with irradiated GM-AML, but not **B7.2**-, IL-4-, or TNF-alpha-AML cells, can elicit leukemia-specific protective and **therapeutic** immunity; and (4) in head-to-head comparison experiments, vaccination with irradiated GM-AML is more potent than B7.1-AML, curing 80% and providing 20% prolonged survival of the leukemic mice at week 2, as opposed to cures only up to 1 week with B7.1-AML vaccines. These preclinical data emphasize that GM-CSF gene immunotherapy deserves clinical evaluation in AML.
Record Date Created: 19980202

4/7/19 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09380173 97376839 PMID: 9233610
The role of donor and recipient B7-1 (CD80) in allograft rejection.
Zheng XX; Sayegh MH; Zheng XG; Li Y; Linsley PS; Peach R; Borriello F; Strom TB; Sharpe AH; Turka LA
Department of Medicine, Beth-Israel Deaconess Medical Center, Boston, MA 02215, USA.
Journal of immunology (UNITED STATES) Aug 1 1997, 159 (3) p1169-73, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI37691, AI, NIAID; AI37798, AI, NIAID

Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Blockade of CD28-mediated T cell costimulatory signals produces effective immunosuppression of a variety of T cell-dependent in vivo immune responses, including autoimmune disorders and transplant rejection. The soluble **fusion protein** CTLA4Ig, which competitively blocks CD28 ligands B7-1 and **B7-2** , can prevent allograft and xenograft rejection and in some circumstances induce transplantation tolerance. To determine the relative roles of B7-1 and B7-2 in graft rejection, we have performed islet and cardiac allografts with normal and B7-1(-/-) mice in conjunction with selective blocking reagents. We found that the absence of B7-1 on donor or recipient tissues leads to a slight prolongation of islet allograft survival, but has minimal or no effect on cardiac allograft survival. Allograft function is further prolonged in the islet model when both donor and recipient lack B7-1, although cardiac allograft survival is not prolonged. In the cardiac model, **treatment** with CTLA4Ig induces long term survival in B7-1(-/-) recipients regardless of donor status. In contrast, anti-**B7-2** mAb leads to indefinite allograft survival only when the recipient and donor both lack B7-1, indicating that even in the absence of available B7-2, B7-1 molecules on the donor or recipient cells alone are sufficient to induce graft rejection. These data also indicate that B7-1 and B7-2 are the only CD28 ligands relevant to cardiac allograft rejection in mice.
Record Date Created: 19970814

4/7/20 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08990132 96320763 PMID: 8739564
Immunosuppression through blockade of CD28:B7-mediated costimulatory signals.
Judge TA; Tang A; Turka LA
Department of Medicine, University of Pennsylvania, Philadelphia 19104-6069, USA.
Immunologic research (UNITED STATES) 1996, 15 (1) p38-49, ISSN 0257-277X Journal Code: IMR
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
It is now well established that T cells require two signals for activation and effector function. The first signal is provided through the T cell receptor for antigen. The best-characterized pathway which provides the second, or costimulatory, signal is through the CD28 receptor on the surface of T cells. In vitro, ligation of the T cell receptor without a second signal induces a long-lived state of anergy in T cells. CD28 has two known ligands, B7-1 and **B7-2** , expressed on activated antigen-presenting cells. A soluble **fusion protein** called CTLA4Ig has been produced which binds B7-1 and **B7-2** and acts as a competitive **inhibitor** of CD28. In vitro and in **vivo** studies with CTLA4Ig demonstrate that it is an extremely effective immunosuppressive agent in models of transplantation and autoimmunity. Mechanistic studies indicate that CTLA4Ig may work by partially inhibiting the expansion of antigen-reactive cells and inducing anergy in the residual population. (34 Refs.)
Record Date Created: 19961024

4/7/21 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

133295356 CA: 133(21)295356j PATENT
Fusion proteins of novel CTLA4/CD28 ligands and uses therefore
INVENTOR(AUTHOR): Freeman, Gordon J.; Nadler, Lee M.; Gray, Gary S.;

Greenfield, Edward
LOCATION: USA
ASSIGNEE: Dana Farber Cancer Institute; Replingen Corporation
PATENT: United States ; US 6130316 A DATE: 20001010
APPLICATION: US 280757 (19940726) *US 101624 (19930726) *US 109393 (19930819) *US 147773 (19931103)
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